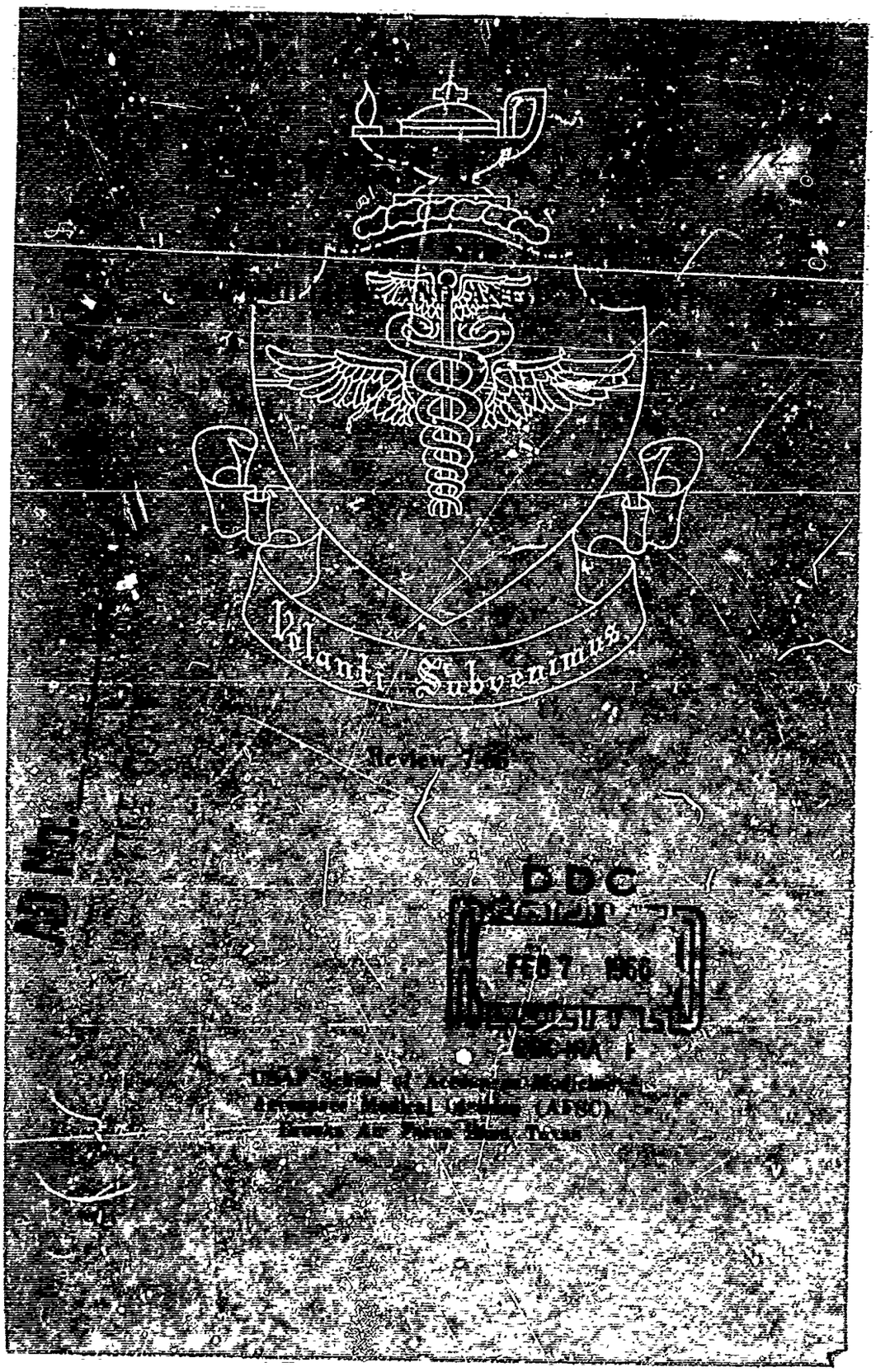
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(6) PHARMACOLOGIC SIDE EFFECTS OF TRANQUILIZERS AND ANTIDEPRESSANTS,

(9) Aeromedical reviews,

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FOREWORD

This review is a summary of a seminar presented at the School of Aerospace Medicine as part of the guest lecture series in November 1964.

The use of trade names in this review is not to be construed as an endorsement of these products by the Air Force. Trade names are used only to aid the reader in the rapid identification of the compounds being discussed.

The assistance of Dr. J. Black and Miss A. De Medici in the preparation of this paper is gratefully acknowledged.

PHARMACOLOGIC SIDE EFFECTS OF TRANQUILIZERS AND ANTIDEPRESSANTS

The subject of side effects of tranquilizers and antidepressants has gained more and more importance during the past decade because of the ever-increasing general use of these drugs. Side effects of an agent acting on the central nervous system actually have spurred Federal legislation supervising the development of new drugs. Everyone knows the unfortunate Thalidomide story.

In psychiatry it is usually quite difficult to find a clear-cut definition for any given subject. This is certainly true for the subject of side effects. The differentiation between neuropharmacologic action as "desirable effect" or "undesirable side effect" is often arbitrary.

The sedative action of the phenothiazines is more pronounced in normal subjects than in psychotics in whom the action is called tranquilizing. Nevertheless, it is presumably the same pharmacologic sedative effect in normal subjects that tranquilizes psychotic patients (1).

Side effects experienced may be of psychosomatic rather than of pharmacologic nature. We, as others, have found in our controlled studies that side reactions are reported during placebo administration. Rickels (2) noted that during the study of a clinically effective agent, frequently, more side reactions are reported from the placebo than from the active agent. Rickels interprets this experience of psychologic side effects such as dizziness, headaches, drowsiness, and others during placebo administration as a passive way for the patient's complaining about the ineffectiveness of the administered compound.

The incidence of psychosomatic side effects is probably highest in patients who suffer from unelaborated, free-floating anxiety, since this is the factor most frequently reported as a characteristic of placebo reactors (3). Naturally, in practice where the welfare of patients is at stake every side effect has to be considered a true pharmacologic side effect until convincingly proved otherwise.

Side effects of psychotropic agents are of two basic types: (1) dose related, and (2) not dose related. Dose-related side effects are due to an extension of the pharmacologic action of the drug—for example, motor restlessness with some antidepressants, or drowsiness and extrapyramidal reactions with tranquilizers. This type of side effect can usually be controlled by lowering of the dosage or administration of suitable concomitant medication. Side effects not dose-related are allergic or toxic reactions such as dermatologic or hepatic manifestations. Side effects of the latter type cannot be predicted on the basis of the pharmacologic action of the drug. The proof of validity for claims of side effects is usually a complicated matter. The elucidation of the mechanisms causing a side effect may be even more complicated or impossible.

TRANQUILIZERS

The older sedatives and hypnotics are not reviewed here since they are different in their pharmacologic action. The tranquilizers may be grouped arbitrarily into phenothiazines, *Rauwolfia* derivatives, and compounds of various structures. Table I lists a few of the more widely used compounds of each group.

The development of tranquilizers began in 1950 with the *Rauwolfia* alkaloids. The story of the use of *Rauwolfia serpentina* (or "snake root") in India for calming agitated people is well known. Perhaps the story began even farther back when Bernthsen in 1883 identified the basic molecular structure of phenothiazine (fig. 1) while working with modifications of methylene blue (4). Phenothiazine in this simple form, although it had

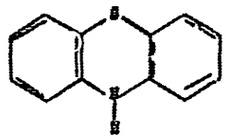
TABLE I

Tranquilizers

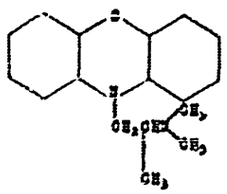
Phenothiazines		
	Phenergan	(promethazine)
	Sparine	(promazine)
	Thorazine	(chlorpromazine)
	Compazine	(prochlorperazine)
	Stelazine	(trifluoperazine)
	Trilafon	(perphenazine)
	Tindal	(acetophenazine)
	Mellaril	(thioridazine)
	Pacatal	(mepazine)
	Permitil	(fluphenazine)
Rauwolfia alkaloids		
	Serpasil	(reserpine)
	Moderil	(rescinnamine)
	Harmonyl	(deserpidine)
Compounds of miscellaneous structure		
	Equanil	(meprobamate)
	Atarax	(hydroxyzine)
	Librium	(chlordiazepoxide)
	Valium	(diazepam)

urinary antiseptic properties, was too toxic for clinical application. It was used as treatment for intestinal worms in sheep in Australia and found some use as an insecticide.

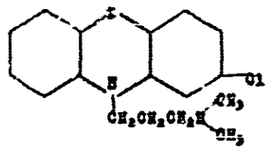
In 1946 promethazine (fig. 1) was developed in France by Halperin as an antihistaminic. It was less toxic than its parent



Basic Phenothiazine Structure



Promethazine (PHENERGAN-Wyeth)



Chlorpromazine (THORAZINE, SKF)

FIGURE 1

and stimulated research into phenothiazines. Various derivatives were created by substitution of the halogen in the 2-position and by modifying side chains.

Chlorpromazine (fig. 1) was the next step in development and a real breakthrough in the chemotherapy of psychiatric illness. Here for the first time was a compound which produced a state of calm and relieved tension without soporific effect or impairment of motor function because it acted on a subcortical level rather than at the cortical sleep-producing level.

The pharmacologic property of the psychoactive phenothiazines is their neuroleptic action (5), that is:

1. Their marked effect on the brain's reticular formation (fig. 2), the limbic system, and the hypothalamus. This reduces psychomotor activity and emotional tension and influences the autonomic system.

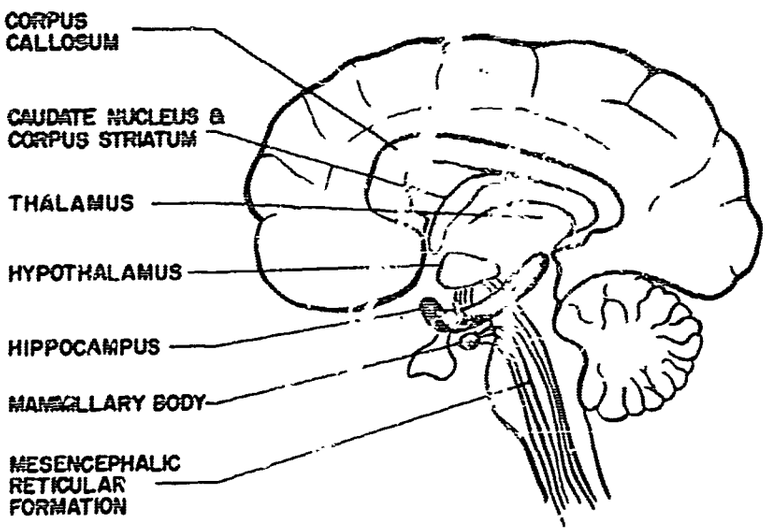


FIGURE 2

2. Their effect on the extrapyramidal system, globus pallidus, and corpus striatum. This causes extrapyramidal symptoms such as Parkinsonism, akathisia, and dyskinesia.

3. A lowering of the convulsive threshold—probably an action on the hippocampus.

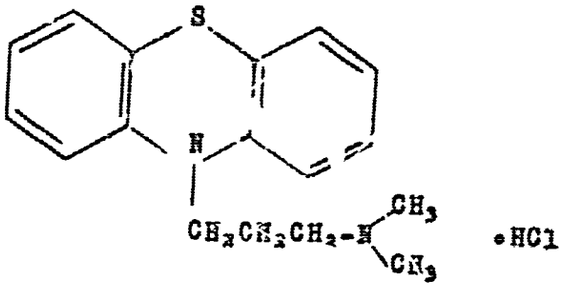
4. Clinically, their antipsychotic action.

The high doses, which were necessary to achieve Thorazine's remarkable effect on psychotics, eventually were found to cause a number of side effects such as agranulocytosis, photosensitivity, hypotension, endocrine effects, autonomic effects, extrapyramidal effects, and jaundice (6). The incidence of jaundice due to Thorazine has steadily decreased, and this fact has given rise to much speculation as to whether the jaundice was a sensitivity reaction or may have been of other origin, possibly viral. Some of the more frequent side effects of widely used tranquilizers are listed in table II with their incidence given in percentage.

TABLE II

Major side effects (percent of cases)

	SCH-6894	Stelazine	Trilafon	Dartal	Compazine	Vesprin	Thorazine	Sparine	Facatal
Extrapyramidal reactions	50	62	20	60	61	30	18	2	0.5
Dermatitis	0	0	0	0	0.5	8	6	4	6
Seizures	0	0	0	0	0.5	0	0.5	4	5



$C_{17}H_{20}N_2S \cdot HCl$

Promazine (SPARINE-Wyeth)

FIGURE 3

In an attempt to avoid the side effects of Thorazine, Promazine (fig. 3) was elaborated by elimination of the chlorine atom in the No. 2 position. However, it was found that potency, rather than side effect, was decreased and related to this chlorine atom; and with the chlorine atom restored, a piperazine ring was added.

This led to the piperazine derivatives (fig. 4) like prochlorperazine (Compazine), perphenazine (Trilafon), trifluoperazine (Stelazine), fluphenazine (Permitil), and others, where potency was increased many times. while the incidence of drowsiness especially, but also jaundice (if real), agranulocytosis, photosensitivity, and autonomic and endocrine effects was reduced. This group, while it has much greater potency, also is more likely to produce extrapyramidal symptoms as shown in table III (7). These extrapyramidal reactions occur most commonly in mental hospitals, where higher doses of the piperazine-ring phenothiazines are used. One bizarre effect occurring with these potent drugs, perhaps once in every thousand patients, is dystonia or muscle spasm, especially in children and especially when they are dehydrated. An anti-Parkinsonian agent or a barbiturate parenterally usually helps in these cases.

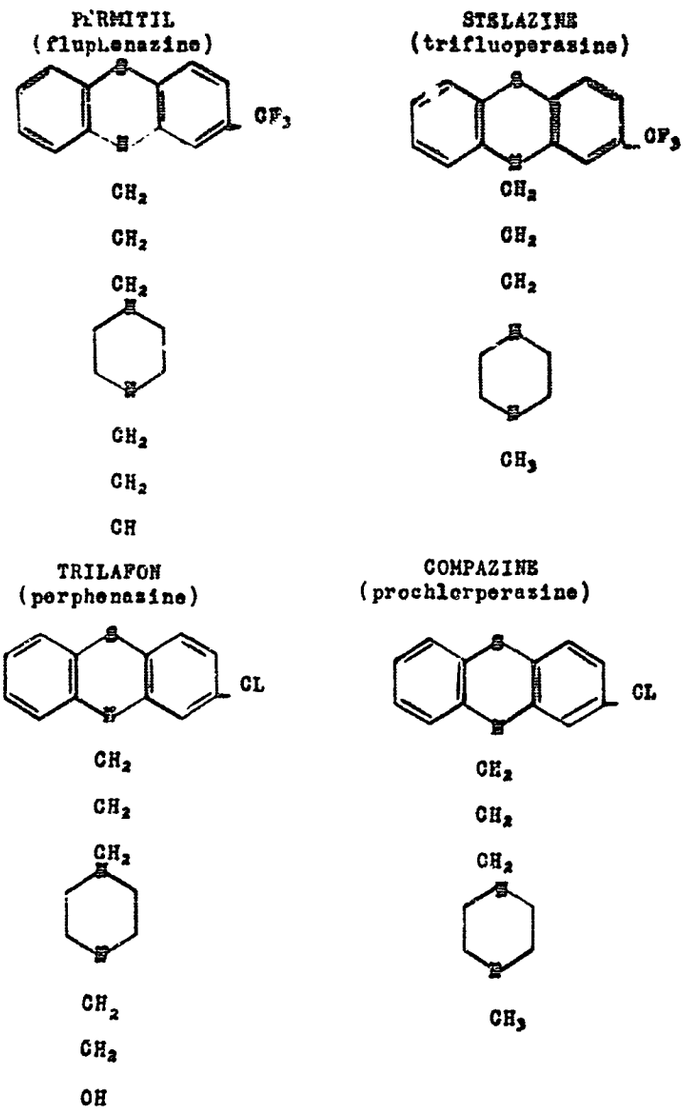
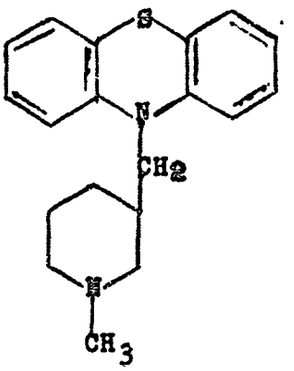


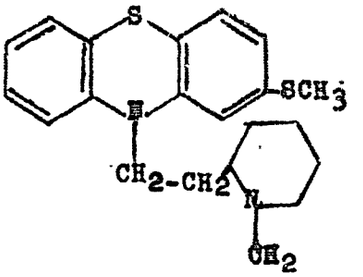
FIGURE 4
Phenothiazine derivatives.

TABLE III

Extrapyramidal reactions (percent of cases)

	SCH-6894	Stelazine	Trilafon	Dartal	Compazine	Vesprin	Thorazine	Sparine	Pacatal
Dosage at which extrapyramidal symptoms may be observed	2 mg.+	4 mg.+	32 mg.+	40 mg.+	60 mg.+	150 mg.+	300 mg.+	400 mg.+	400 mg.+
Parkinsonism	16	22	15	17	20	16	14	0.5	0.5
Dyskinesia	12	8	1	2	2	3	0.5	0	0
Motor restlessness	30	30	20	25	21	17	20	1.5	0.5





mepazine (PACATAL)

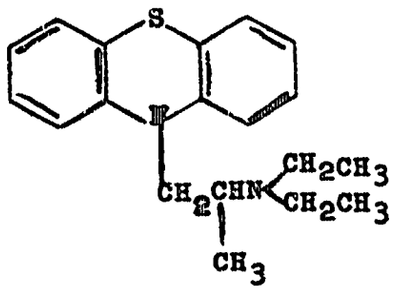
thioridazine (MELLARIL, SANDOZ)

FIGURE 5

The piperidyl derivatives are the next development in the phenothiazine group with the characteristic of particularly low incidence of extrapyramidal symptoms. Mepazine (Pacatal) and thioridazine (Mellaril) are in this group (fig. 5).

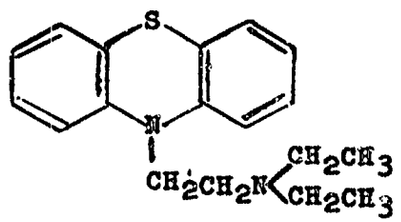
The phenothiazines are a versatile group of compounds. Although they produce Parkinsonism as a side effect, some of them—such as (fig. 6) diethazine (Diparcol) and ethopropazine (Parsidol)—are used in the treatment of Parkinsonism. The forerunner of the phenothiazine tranquilizers, promethazine (Phenergan), finds wide use as a sedative-antihistamine. Phenothiazines also used as antiemetics for nausea of central origin are Compazine and Trilafon.

Phenothiazines in general are antagonistic to acetylcholine. In contrast to reserpine tranquilizers, they cause no parasympathetic



ethopropazine

(PARSITAN, formerly PARSIDOL, Warner Chilcott)



diethazine

(DIPARCOL, May & Baker)

FIGURE 6

TABLE IV

Phenothiazine—side effects

Central nervous system	**Endocrine effects**
Behavioral effect (sedation)	Disturbances of menstruation
Extrapyramidal syndrome	Artificially induced lactation, gynecomastia
Akinesia	Pseudopregnancy response
Dyskinesia	Disturbed sexual function
Akathisia	Disturbance of glucose metabolism
Parkinsonism	Edema
Autonomic nervous system	Weight gain
Cardiovascular disturbance	**Allergic or toxic reactions**
Dizziness, faintness, weakness	Cholestatic jaundice (biliary cirrhosis)
Sweating	Agranulocytosis
Dryness of mouth, throat	Other blood dyscrasias
Nausea, vomiting	Dermatologic manifestations
Increased salivation	**Miscellaneous**
Constipation	Death
Diarrhea	Anesthetic complications (blocked pressor reflexes)
Urinary disturbance	Electrocardiographic abnormalities
Blurred vision	Potentiation of other drugs
	Pigmentary retinopathy
	Melanin pigmentation

side effects. The more common side effects are listed in table IV. Endocrine effects of the phenothiazines are manifested by lactation (8), gynecomastia, menstrual irregularities, false pregnancy test (10), and reduction in urinary gonadotropin. The estrogenic

effect may cause impotency in men and increased libido in women. Reassurance is the treatment of choice here.

One side effect of phenothiazines is their potentiating effect on sedatives and hypnotics. This side effect is frequently made a useful adjunct when phenothiazines are prescribed in preparation for or after surgery. Great caution is indicated here, however, because the blocking action of phenothiazines on the pressor-reflex may cause anesthetic complications in the nature of a hypotensive collapse. Also, the CNS depression added to compounds such as Demerol may cause respiratory depression and bulbar paralysis.

Another side effect associated with phenothiazine therapy is the cardiac toxicity. Ban and St. Jean (11) recently described a study where thioridazine, chlorpromazine, and trifluoperazine were administered to six psychiatric patients. Each agent was used in four dosage levels. The findings indicated that thioridazine modifies the terminal portion of the human ECG (e.g., the S-T segment, T and U waves). A similar change occurred in three of six subjects while taking chlorpromazine and in one of six who were taking trifluoperazine.

Graupner and Murphree (12) also described nonspecific electrocardiographic changes after thioridazine administration. The electrocardiographic changes are not accompanied by clinical evidence of heart disease and the present findings suggest that the changes are reversible upon discontinuance of reduction of the drug. Kelly et al. (13) reported on two patients who died while receiving large doses of thioridazine (1,500 and 3,600 mg. daily, respectively). Terminal ECG patterns showed heart block alternating with episodes of ventricular tachycardia. Because of this influence on the ECG, it is recommended to obtain ECG's before starting patients on thioridazine therapy so that complaints of cardiac symptoms can be checked and followup ECG's can be properly interpreted.

Another side effect reported with thioridazine (Mellaril) (14) and other phenothiazines (15) is pigmentary retinopathy, when high doses are administered. The symptoms are diminution of

visual acuity and impairment of night vision. Greiner and Nicolson (16) have described extensive deposits of pigment (exhibiting the physical and histochemical properties of melanin) after prolonged chlorpromazine therapy. This occurred in the dermis and throughout the reticuloendothelial system, and in the parenchymal cells of internal organs. The patients were twelve physically healthy young individuals who died unexpectedly while on chlorpromazine therapy. Obvious pigmentation of the unexposed skin was seen in five of these patients.

Thioridazine (Mellaril) has more adrenergic blocking effects than other phenothiazines, therefore decreasing the blood pressure more often. Inhibition of ejaculation (9) is also a side effect owing to the adrenergic blocking action. Two other side effects of phenothiazines, which were reported in the literature, are a diabetogenic action (17) and an influence on the PBI (18). The diabetogenic action has not been confirmed, and the influence on the PBI is disputed (19). Teratogenic influences with phenothiazines as with other psychotropic drugs have been reported in Canada, England, and Australia (20), but the incidence of teratogenic effects seems to be no greater in patients taking psychotropic drugs than in the average population.

The next group of tranquilizers comprises the *Rauwolfia* alkaloids. Representative structures of these are given in figure 7. These drugs cause effects which resemble depression of the sympathetic nervous system and stimulation of the parasympathetic nervous system centrally as well as peripherally. Reserpine causes a depletion of norepinephrine and serotonin in the brain (1). *Rauwolfia* alkaloids are only seldom used in psychiatric indications since the advent of phenothiazines, but continue to have a place in the treatment of hypertension in combination with diuretics.

Table V shows some of the more common side effects of *Rauwolfia* alkaloids. Hypotension is listed as a side effect here, where the indication is the treatment of presumably normotensive psychotics. Other adverse effects are sedation, mental depression sometimes leading to suicide, paranoid ideation, and extrapyramidal reactions (21). Autonomic effects include swelling of the

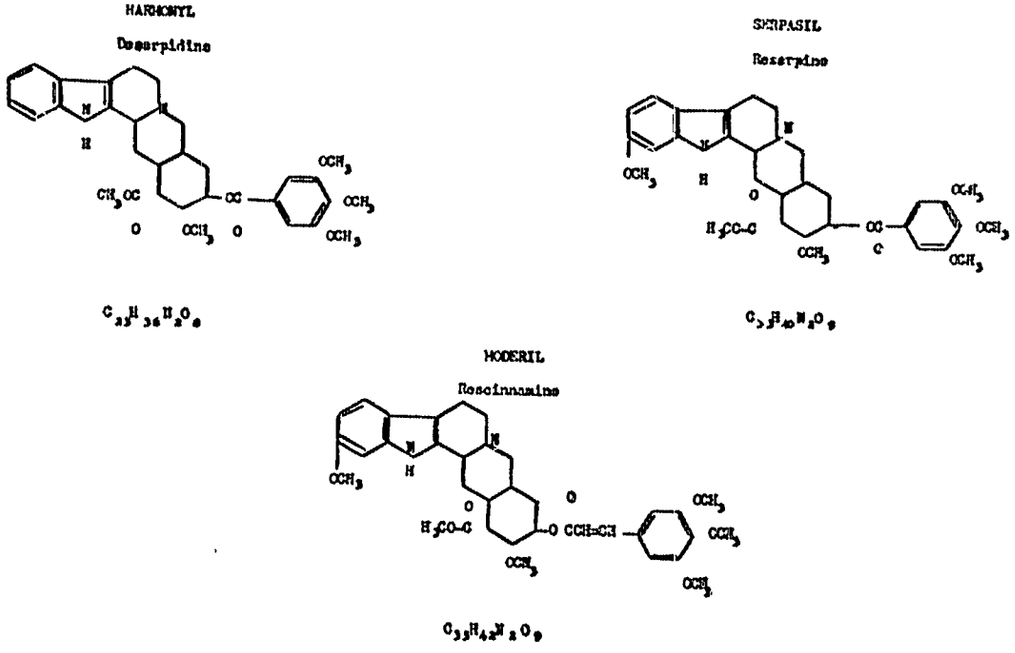


FIGURE 7
Rauwolfia *alkaloids.*

TABLE V

Rauwolfia—*side effects*

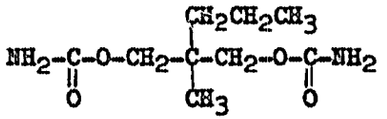
Central nervous system
Sedation
Mental depression, paranoid and suicidal tendencies
Extrapyramidal reactions
Autonomic nervous system—toxic effects
Stuffy nose
Hypotension
Cardiac arrhythmia
Diarrhea
Hyperacidity, peptic ulcer

nasal turbinates (stuffy nose), miotic pupils, cardiac arrhythmia, hyperacidity, and disturbances of the temperature regulation. In the male, *Rauwolfia* alkaloids can cause feminizing effects, loss of libido, and impotence (22).

The last group of tranquilizers contains compounds of various structures shown in figure 8. Meprobamate, hydroxyzine, chlordiazepoxide, and diazepam are often referred to as "minor tranquilizers." Their use is in anxiety-tension states rather than in psychosis.

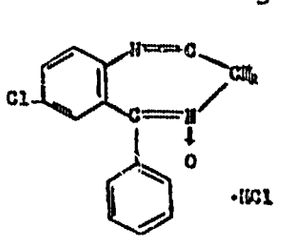
Table VI lists some side effects connected with these compounds. In their effect these compounds have been likened to the older sedatives and they are used largely as substitutes for phenobarbital. Most used in this class are meprobamate and Librium. The major side effect of the former is sedation; indeed, some claim that this is the sole action of the agent. The majority opinion charges some additional action to the compound, although certainly the margin between calming the anxious patient and sedation as a side effect is not large. Meprobamate has caused non-thrombocytopenic purpura and skin rashes. While in the recommended doses side effects are reasonably few with this compound, its addiction liability is very real; the calm dysarthric

EQUANIL, MILTOWN (Meprobamate)



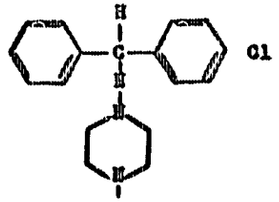
$C_9H_{18}N_2O_4$

LIBRIUM (Chlordiazepoxide)



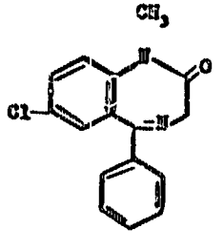
$C_{16}H_{14}ClN_3O \cdot HCl$

ATARAX, VISTARIL (Hydroxyzine)



$C_{21}H_{27}ClN_2O_2 \cdot 2HCl$ or
$\cdot C_{23}H_{16}O_6$

VALIUM (Diazepam)



$C_{16}H_{13}ClN_2O$

Tranquilizers. Compounds of miscellaneous structure.

TABLE VI

Tranquilizers of miscellaneous structure—side effects

Meprobamate (Miltown)	
	Drowsiness
	Habituation
	Withdrawal reactions (convulsions, tremor)
	Non-thrombocytopenic purpura
	Dermatologic reactions
Hydroxyzine (Atarax)	
	Drowsiness
	Dry mouth
	Mildly anticoagulant—potentiating
	Involuntary motor activity at high dosage
Chlordiazepoxide (Librium)	
	Paradoxical excitement
	Judgment defect (car accidents)
	Ataxia
Diazepam (Valium)	
	Drowsiness
	Ataxia
	Mild nausea
	Withdrawal symptoms (convulsions, tremor)

individual who is always tired may be a meprobamate addict. "Miltini's" (Martinis and a Miltown) are fashionable in some circles. Meprobamate withdrawal can cause reactions with tremor and convulsions. Librium can cause paradoxical excitement and ataxia (23). It has been reported to affect automobile driving adversely because of poorer judgment, decreased visual acuity, and exophoria (24). While meprobamate has been taken in suicidal doses, Librium is relatively safe when taken in excess even at doses of 2,250 mg. concurrent with alcohol (25). Side effects of Valium are generally the same as for Librium. Hydroxyzine (Atarax) may cause involuntary motor activity at high doses. It has been observed in some patients receiving concurrent anticoagulant therapy to decrease the required anticoagulant dosage (26).

TABLE VII

Antidepressants

Amphetamines	
Benzedrine	(amphetamine)
Dexedrine	(dextroamphetamine)
Desoxyn	(metamphetamine)
Piperidyl derivatives	
Ritalin	(methylphenidate)
Meratran	(pipradol)
MAO-I's (hydrazine derivatives)	
Marplan	(isocarboxazid)
Nardil	(phenelzine)
Niamid	(nialamide)
MAO-I's (non-hydrazine derivatives)	
Parnate	(tranylcypromine)
Iminodibenzyl derivatives	
Tofranil	(imipramine)
Elavil	(amitriptyline)

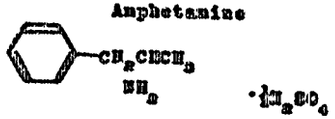
ANTIDEPRESSANTS

Antidepressants may be grouped (table VII) into: (1) amphetamines, which are sometimes referred to as psychoenergizers—including Benzedrine, Dexedrine, and Desoxyn; (2) piperidyl derivatives, which are Ritalin and Meratran; (3) MAO Inhibitors, which are divided into hydrazine derivatives like Marplan, Nardil, and Niamid and into non-hydrazine derivatives like Parnate, and (4) the iminodibenzyl derivatives, such as Tofranil and Elavil.

Figure 9 shows two amphetamine structures. Amphetamine evolved from sympathomimetics by change of the epinephrine molecule. Further molecular modification led to methylphenidate (Ritalin). The amphetamines were stimulants and only mildly antidepressant.

Benzedrine

Amphetamine



$C_9H_{13}N \cdot \frac{1}{2}H_2SO_4$

Dexedrine

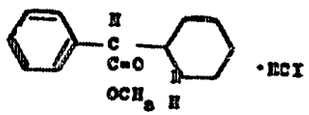
d-amphetamine

$C_9H_{13}N \cdot \frac{1}{2}H_2SO_4$

Piperidyl Derivative

Ritalin

Methylphenidate



$C_{14}H_{19}NO_2 \cdot HCl$

FIGURE 9

Amphetamines.

TABLE VIII

Antidepressants—side effects

Amphetamines
Euphoria
Hypertension
Insomnia
Anxiety and jitteriness
Anorexia
Palpitation
Piperidyl derivatives (Ritalin)
Motor restlessness – insomnia
Anorexia—nausea
Tachycardia
Vertigo
Headache
Hypertension

Most frequent side effects (table VIII) include euphoria, hypertension, insomnia, anorexia, and palpitation (27). Also, the stimulatory phase was followed by a depressive phase and tolerance developed. Ritalin was an improvement in that it produced less anorexia, insomnia, and euphoria than amphetamines. A shock-like condition, however, has been reported with tremor, sweating, tachycardia, headache, vertigo, and motor restlessness. Ritalin is sometimes used to counteract the lethargy associated with some tranquilizers.

The next step in the development of antidepressants was the discovery of MAO Inhibitors. The first hydrazine compound to exhibit antidepressant action was Marsilid, which originally was administered as a tuberculostatic drug. During treatment for

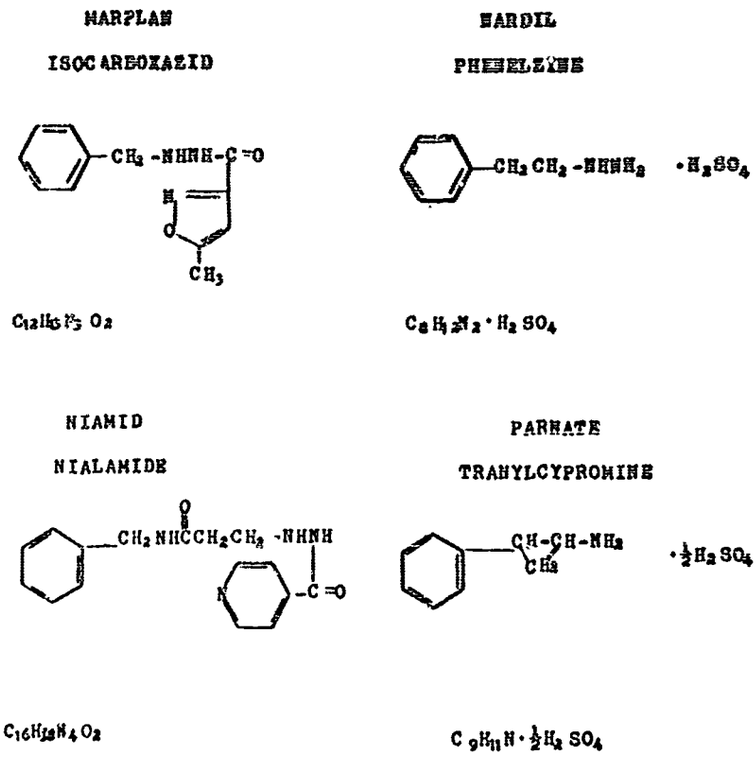


FIGURE 10

MAO Inhibitors.

tuberculosis the patients began to be less depressed, and this led Klein (28) to the use of Marsilid in depressed patients in psychiatry. Because of its liver toxicity and a host of other side effects, Marsilid was withdrawn from the market. MAO Inhibitors now in use include the hydrazine derivatives—Marplan (isocarboxazid), Nardil (phenelzine sulfate), Niamid (nialamide) and Pargyline (eutonyl)—and the non-hydrazine derivative, Parnate (tranylcypromine) (fig. 10). These MAO Inhibitors are very potent antidepressants.

TABLE IX

MAO-Inhibitors—side effects

CNS—side effects
Motor restlessness, mania, hypomania
Converting retarded depression to agitated depression
Precipitating psychosis
Insomnia
Synergistic effect with imipramine, amitriptyline, amphetamine, alcohol, Demerol, and others
Restlessness, muscle twitching, and convulsions
Hyperpyrexia
Potentiation by tyramine in food
Hypertension, headache, stiff neck, nausea, vomiting, intracranial hemorrhage
Autonomic side effects
Orthostatic hypotension
Dizziness and vertigo
Constipation
Dry mouth
Blurred vision
Interference with ejaculation
Toxic and allergic reactions
Hepatocellular damage (hydrazines)

Side effects include (table IX) central nervous system manifestations like motor restlessness, mania, hypomania, insomnia, the conversion of retarded depression to an agitated depression, and sometimes the precipitation of a latent psychosis (29). Because of the synergistic effect of the MAO Inhibitors with imipramine (30), amitriptyline, amphetamine, Demerol, and others (31), the concomitant administration of these is contraindicated.

Extreme caution has to be exercised if a patient is changed from an MAO Inhibitor to one of these drugs; a two-week interim between drugs is desirable. Manifestations of a synergistic effect are restlessness, muscle twitching, convulsions, and hyperpyrexia. Another side effect—especially of Parnate (tranylcypromine), the most potent of the MAO Inhibitors—is the potentiation of its effect by tyramine in food. Especially high tyramine contents were found in aged cheeses (32) and Chianti wine, which contains 25 μg. of tyramine per milliliter. Parnate had been taken off the market some time ago because of this potentiating effect and has only recently been reinstated. Symptoms relating to a potentiating effect of tyramine, which is a pressor agent with 2% to 5% of the activity of epinephrine, are paradoxic hypertension, headache, stiff neck, nausea, vomiting, and—in several reported cases—intracranial hemorrhage, and death.

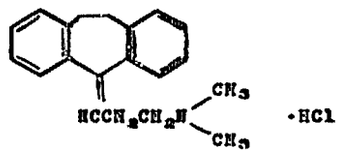
Autonomic side effects of MAO Inhibitors include orthostatic hypotension, dizziness and vertigo, constipation, dry mouth, blurred vision, and interference with ejaculation. Agranulocytosis also is a side effect of the MAO Inhibitors and a toxic side effect, especially of the hydrazine group, is hepatocellular damage.

The last group comprises antidepressants derived from antihistamines and tranquilizers. These structures (fig. 11) are similar to the earlier shown phenothiazine structures. Amitriptyline and imipramine are the only compounds of this so-called iminodibenzyl-derivative group being widely used.

Side effects for imipramine and amitriptyline (table X) (35) include central nervous system manifestations such as tremor, especially of the tongue and hand, muscle twitching, and paresthesias (36). Peroneal palsies have been reported. Autonomic side effects are anticholinergic in nature (more pronounced with amitriptyline than with imipramine). They are aggravation of glaucoma, disturbances of accommodation, dry mouth, tachycardia, constipation, urinary retention, and orthostatic hypotension (37). Both amitriptyline and imipramine have an effect on the electrocardiogram (38). They cause flattened T-waves, prolonged Q-T intervals, and depressed S-T segments when given in

Elavil

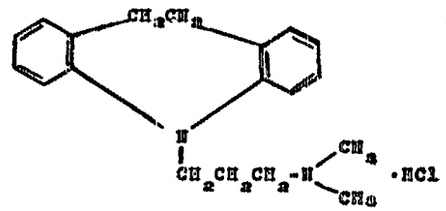
Amitriptyline



$C_{20}H_{23}N \cdot HCl$

Tofranil

Imipramine



$C_{19}H_{24}N_2 \cdot HCl$

FIGURE 11

Antidepressants derived from antihistamines and tranquilizers.

TABLE X

Imipramine and amitriptyline—side effects

CNS—side effects
Sedation
Weakness and fatigue
Excitement
Tremor
Autonomic side effects
Dry mouth
Tachycardia
Constipation
Disturbance of accommodation
Urinary retention
Orthostatic hypotension
Other side effects for imipramine
Myocardial infarction (suicidal doses)

ordinary therapeutic doses (29). Myocardial infarction has also been reported with suicidal doses.

An enumeration of side effects such as this makes the psychotropic agents appear to be very dangerous drugs. Indeed, the more powerful of these agents are very dangerous, and constant vigilance during their administration is essential. In practice, one should always try to get by with one of the less powerful agents. In taking recourse to the more powerful psychotropic drugs, one has to weigh the expected benefits against the risks attendant on their administration.

REFERENCES

1. DiPalma, J. R. The basic pharmacologic principles underlying the use of sedatives and tranquillizers. Clin. Pediatrics 2:225 (1963).

2. Rickels, K. Controlled out-patient studies with "Non-Psychotic Psychiatric Patients," vol. 5, p. 103. Transactions of the Fifth Research Conference on Cooperative Chemotherapy Studies in Psychiatry and Research Approaches to Mental Illness, 6-8 June 1960. Washington, D.C.: Veterans Administration, Dec. 1960.

3. Shapiro, A. K. Etiological factors in placebo effect. J. A. M. A. 187:713 (1964).

4. Black, J. Phenothiazines as antiemetics and tranquilizers. J. Med. Ass. Alabama 29:3 (1960).

5. Himwich, H. E. Tranquilizers, barbiturates and the brain. J. Neuropsychiat. 3:279-94 (1962).

6. Ayd, F. J., Jr. Phenothiazine tranquilizers: Eight years of development. Med. Clin. N Amer. 45:1027-1040 (1961).

7. Ayd, F. J., Jr. A survey of drug-induced extrapyramidal reactions. J. A. M. A. 175:1054 (1961).

8. Hooper, J. H., Jr., V. C. Welch, and R. T. Shackelford. Abnormal lactation associated with tranquilizing drug therapy. J. A. M. A. 178:506-507 (1961).

9. Freyhan, F. A. Loss of ejaculation during Mellaril treatment. Amer. J. Psychiat. 118:171-172 (1961).

10. King, J. T., M. C. Barry, and E. R. Neary. Perinatal findings in women treated during pregnancy with oral fluphenazine. J. New Drugs 3:21-25 (1963).

11. Ban, T. A., and A. St. Jean. The effect of phenothiazines on the electrocardiogram. Canad. Med. Ass. J. 91:537 (1964).

12. Graupner, K. I., and O. D. Murphree. Electrocardiographic changes associated with the use of thioridazine. J. Neuropsychiat. 5:344 (1964).

13. Kelly, H. G., J. E. Fay, and S. G. Laverty. Thioridazine hydrochloride (Mellaril): Its effect on the electrocardiogram and a report of two fatalities with electrocardiographic abnormalities. Canad. Med. Ass. J. 89:546 (1963).

14. Weekly, R. D., A. M. Potts, J. Reboton, and R. H. May. Pigmentary retinopathy in patients receiving high doses of a new phenothiazine. Arch. Ophthal. (Chicago) 64:65-76 (1960).

15. Reboton, J., Jr., R. D. Weekly, N. D. Rylenga, and R. H. May. Pigmentary retinopathy and irido-cycloplegia in psychiatric patients. J. Neuropsychiat. 3:311-316 (1962).

16. Greiner, A. C., and G. A. Nicolson. Pigment deposition in viscera associated with prolonged chlorpromazine therapy. Canad. Med. Ass. J. 91:627-635 (1964).

17. Arneson, G. A. Phenothiazine derivatives and glucose metabolism. J. Neuropsychiat. 5:181-185 (1964).

18. Cranswick, E. H., G. M. Simpson, and A. Nies. An abnormal thyroid finding produced by a phenothiazine. J. A. M. A. 181:554-555 (1962).

19. Hollister, L. E., and J. L. Bennett. Thyroid function and psychotherapeutic drugs. J. A. M. A. 185:890 (1963).

20. Refshauge, W. D. Phenmetrazine and trifluoperazine. Med. J. Aust. 1:58 (1963).

21. Cattell, J. P., and S. Malitz. Revised survey of selected psychopharmacological agents. Amer. J. Psychiat. 117:449-453 (1960).

22. Cares, R. M., and C. Buckman. Comparative review of the structure and side effects of newer psychotropic agents. Dis. Nerv. Syst. 24:92-105 (1962).

23. Murray, N. Covert effects of chlordiazepoxide therapy. J. Neuropsychiat. 3:168-170 (1962).

24. Miller, J. G. Objective measurements of the effects of drugs on driver behavior. J. A. M. A. 179:940-943 (1962).

25. Zbinden, G., R. E. Bagdon, E. F. Keith, R. D. Phillips, and L. O. Randall. Experimental and clinical toxicology of chlordiazepoxide (Librium). Toxicol. Appl. Pharmacol. 3:619-637 (1961).

26. Physician's desk reference, 1964 Roergi & Co., J. B. Prof. Products Information, p. 846.

27. Caffey, E. M., Jr., and C. J. Klett. Side effects and laboratory data, vol. 5, p. 23. Transactions of the Fifth Research Conference on Cooperative Chemotherapy Studies in Psychiatry and Research Approaches to Mental Illness, 6-8 June 1960. Washington, D. C.: Veterans Administration, Dec. 1960.

28. Loomer, H. P., J. C. Saunders, and N. S. Kline. A clinical and pharmacodynamic evaluation of ipromiazid as a psychic energizer. Washington, D. C.: Psychiatric Research Reports of the American Psychiatric Association, No. 8, p. 129, 1957.

29. Hollister, L. E. Complications from psychotherapeutic drugs-1964. Clin. Pharmacol. Ther. 5:322-333 (1964).

30. Harrer, G. Incompatibility between MAO Inhibitors and imipramine. Wien. Med. Wschr. 111:551 (1961).

31. Eichhorn, O. Contribution on problem of incompatibility of corabinations of various psychotropic substances. Wien. Med. Wschr. 111:553 (1961).

32. Asatoor, A. M., A. J. Levi, and M. D. Milne. Letters to the editor. Lancet 2:733 (1963).

33. Lees, F., and C. W. Burke. Tranylcypromine. Lancet 1:13-16 (1963).

34. Council on Drugs. Paradoxical hypertension from tranylcypromine sulfate. J. A. M. A. 186:854 (1963).

35. Kane, F. J., Jr. Toxic reactions to antidepressant drugs. Southern Med. J. 57:691 (1964).

36. Cares, R. M., and C. Buckman. A survey of side-effects and/or toxicity of newer psychopharmacologic agents. Dis. Nerv. Syst. 22:97-106 (1961).

37. Wortis, J. Psychopharmacology and physiological treatment. Rev. Psychiatric Progress, pp. 643-648 (Jan. 1964).

38. Edwards, A. L. Imipramine myocardial toxicity. New York J. Med. 64:1979-1982 (1964).

Manufacturer	*Drug*
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	Marsilid
	Valium
Roerig	Atarax
Sandos	Mellaril
Schering	Trilafon
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